The Effects of Coffee Intake on Survival in Metastatic Colorectal Cancer

The Effects of Coffee Intake on Survival in Metastatic Colorectal Cancer:

Results from CALGB/SWOG 80405 (Alliance), 2016

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Abstract

Previous studies have identified associations between dietary and lifestyle factors and the incidence, risk of recurrence, and mortality of colorectal cancer. The consumption of coffee is one such factor that has been positively associated with improved prognosis in colorectal cancer patients, a finding that has been supported by both epidemiological and laboratory-based *in vivo* and *in vitro* studies. Using data collected as part of a national phase III randomized clinical trial (CALGB/SWOG 80405), we conducted a prospective epidemiological study of the effects of coffee consumption on survival in metastatic colorectal cancer patients. To our knowledge, this is the first study to examine the prognostic impact of coffee consumption in patients with metastatic colorectal cancer. Among this cohort of patients, we detected a significant inverse association between the increasing consumption of coffee and a decreased hazard of both cancer progression and death from any cause. Participants who consumed 4 or more cups of coffee per day had an adjusted hazard ratio for overall mortality of 0.62 (95% CI, 0.43 to 0.89; Ptrend = 0.008) and an adjusted hazard ratio for disease progression or death of 0.71 (95% CI, 0.52 to 0.98; Ptrend = 0.04). These findings were consistent across strata of demographic, clinical, and disease characteristics, and a significant interaction was noted between coffee consumption and adherence to a healthy 'prudent' dietary pattern ($P_{interaction}$ = 0.01). Our results suggest a role for coffee consumption in the prognosis of patients with colorectal cancer, possibly mediated by its anti-oxidant and anti-inflammatory properties, or effects on insulin-sensitizing pathways. Further research is warranted to fully characterize these possible underlying mechanisms.

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Chapter I

Introduction

Despite advances in both treatment and detection, colorectal cancer remains a common and deadly disease in the United States. A large proportion of affected patients are diagnosed with metastatic disease at the time of clinical presentation or will ultimately develop distant metastases (Kindler & Shulman, 2001). Among these metastatic patients, median survival remains at approximately two years from diagnosis, and fewer than 6% of patients will survive for more than five years (Edge, 2010). It is clear that more needs to be done to improve the prognosis for patients diagnosed with this disease.

A number of previous studies have linked dietary and other lifestyle factors to the incidence of colorectal cancer (Cross et al., 2010; Hartz et al., 2012) and the risk of cancer recurrence after surgical resection of stage I-III disease (Meyerhardt et al., 2007; Meyerhardt et al., 2012; Fuchs et al., 2014). For example, a recent study found a correlation between higher intake of caffeinated coffee and significantly reduced cancer recurrence and death in patients with stage III resected colon cancer (Guercio et al., 2015). Various factors associated with an unhealthy lifestyle, such as higher BMI or more frequent alcohol consumption, have been correlated with increased risk of colon cancer related death (Chong et al., 2015). Though the molecular mechanisms underlying these factors are still largely unknown, there are clearly links between patients' lifestyles and the pathogenesis of this disease.

Less is known about the effects of such lifestyle factors in patients with metastatic colorectal cancer, although it is a great area of interest among patients diagnosed with this disease and the oncologists caring for them. A recent prospective epidemiological study found

a positive correlation between metastatic colorectal cancer patients' plasma 25-hydroxyvitamin D levels prior to initiating first-line palliative chemotherapy and the duration of their progression free and overall survival (Ng et al., 2015). *In vivo* studies have found that a high fat 'Western' diet up-regulates the EGFR pathway (Dougherty et al., 2015), and other factors such as green tea, ginseng, and curcumin down-regulate the same pathway (Pabla, 2015). Ginseng in particular was shown to suppress the growth of colon tumors in xenografts (Pabla, 2015). Each of these findings suggests a potential for dietary consumption and other lifestyle factors to modify oncogenic processes associated with the growth and spread of cancer and its associated mortality.

Recently, the consumption of coffee has garnered increasing interest. As cited above, a prospective epidemiological study published in 2015 used dietary data collected as part of CALGB/Alliance study 89803 to examine the influence of coffee, non-herbal tea, and caffeine intake on cancer recurrence in patients with resected stage III colon cancer. The study found that higher coffee intake was associated with significantly reduced cancer recurrence and death in this patient population (Guercio et al., 2015). Additionally, a randomized study showed a decreased risk of hepatocellular carcinoma among hepatitis C patients who consumed 4 cups of coffee per day compared to a control group that abstained from coffee (Cardin et al., 2013), and an *in vitro* study showed anti-tumor cell activity associated with kahweol, a diterpene molecule found in coffee beans (Choi et al., 2015). These data suggest that coffee may have a potential anti-cancer effect, though to our knowledge the effect of coffee consumption in patients with metastatic colorectal cancer has not been studied.

In light of these promising data, we conducted a prospective epidemiological study evaluating the influence of coffee and tea consumption on survival in patients with metastatic

colorectal cancer. Prospective data collected as part of a completed phase III randomized clinical trial, CALGB/SWOG 80405, was used to examine this question. We examined differences in progression free survival and overall survival in metastatic colorectal cancer patients according to their daily consumption of coffee and tea. Our hypothesis was that patients who consumed more coffee would demonstrate longer progression free survival and overall survival compared to those who consumed less coffee. We additionally evaluated this association in subgroups of metastatic colorectal cancer patients stratified by known prognostic clinical and disease characteristics.

Definition of Terms

"Adiponectin": a protein hormone involved in glucose metabolism that is secreted by adipocytes (fat cells)

"Alliance/CALGB": a national NCI-funded cooperative research group that focuses on cancer treatment and clinical research

"C-peptide": a short amino acid chain that is part of the structure of proinsulin, the precursor molecule to insulin

"EGF(R)": Epidermal Growth Factor (Receptor); a ligand and membrane bound receptor involved in cell growth and frequently implicated in the proliferation of cancer cells

"IGF-1": Insulin-like Growth Factor 1, a hormone that is similar in structure to insulin and associated with growth in adults; previous studied have linked high IGF-1 levels to cancer risk and survival

"Insulin": a hormone associated with glucose metabolism; several related molecules have been associated with risk of colon cancer

"*In vivo*": refers to experiments conducted in animal models

"*In vitro"*: refers to experiments conducted in cell cultures

"Overall Survival": length of time that a patient survives after diagnosis with a disease; frequently used as a marker of cancer treatment efficacy

"Progression Free Survival": length of time that a patient's cancer remains radiologically and/or clinically stable; frequently used as a marker of cancer treatment efficacy

"Recurrence": a return of detectable cancer after curative-intent surgery or other interventions

"Xenograft": in cancer research, refers to an animal model in which human cancer cells are grown in a lab animal, frequently an immunosuppressed mouse

Background

Colorectal Cancer

Colorectal cancer is the third most common cancer and second most common cause of cancer related death in the United States (American Cancer Society, 2013). While early detection can lead to improved patient outcomes as a result of curative surgery, 15 to 25% of patients are diagnosed with metastatic disease and a large proportion will ultimately develop metastases (Kindler & Shulman, 2001). Once metastatic disease is found, the cancer is no longer considered curable and treatment instead focuses on palliation of symptoms and extension of life. Recently developed targeted therapies and novel chemotherapeutic agents have modestly improved survival in this population (Cleghorn, 2015; Cutsem et al., 2015). However, the median survival time remains at 2 years and fewer than 6% of patients survive for greater than 5 years (Edge, 2010). While there is ongoing research to develop innovative pharmaceutical treatments for this disease, lifestyle modification may have a significant impact on prognosis when used in combination with current modalities, and offers the potential for clinical benefit without the cost and toxicities associated with standard therapies.

Lifestyle Influences on Colorectal Cancer

A number of previous studies have demonstrated relationships between lifestyle factors and the risk of colon cancer incidence and recurrence. Specifically, body-mass index, physical activity level, alcohol and tobacco use, and the consumption of red meat have been associated with the risk of developing colorectal cancer and/or the risk of recurrent cancer after surgical intervention (Meyerhardt et al., 2007; Meyerhardt et al., 2012; Fuchs et al., 2014; Cross et al., 2010; Hartz et al., 2012). In some cases these associations are quite dramatic. A study in 2014 found that patients with stage III colon cancer who consumed 2 or more servings of sugar-sweetened beverages per day nearly doubled their relative risk of cancer recurrence after surgical resection (Fuchs et al., 2014). Another study in stage III colon cancer patients found decreased risk of cancer recurrence and longer overall survival in patients who consumed a healthier 'prudent' diet compared to a higher fat 'western' diet. This effect was biologically compelling due to its dose dependent nature – extreme ends of the prudent vs. western spectrum were the most strongly correlated with changes in risk of recurrence and mortality (Mayerhardt et al., 2007). Similarly, a positive correlation has been found between dietary glycemic load and colon cancer recurrence, and a negative correlation between weekly exercise hours and colon cancer recurrence (Meyerhardt et al., 2012; Michaud et al., 2001). An analysis of known cancer risk factors estimated that if all 40-year-old males maintained a normal BMI, exercised for at least 15 hours per week, took a daily multivitamin, ate fewer than 3 servings of red meat per week, drank less than 1 serving of alcohol per day, and abstained from tobacco, 71% of colorectal cancer cases could be prevented (Platz et al., 2000).

Other research has implicated specific foods and nutrition-related compounds in improvement of colorectal cancer outcome. 25-hydroxyvitamin D is an intriguing molecule which has been shown to reduce cancer growth and metastases *in vivo* and which may be a predictor of colorectal cancer survival in humans (Rossdeutscher et al., 2014; Ng et al., 2015). The wealth of data regarding the relationship between Vitamin D and colorectal cancer has led to several clinical trials investigating the effects of supplementing patients with high doses of vitamin D. Similarly, ginseng and curcumin have been shown to down-regulate the EGFR pathway *in vivo* and some data suggests the potential for these and other compounds to slow the growth of cancers *in* vivo (Pabla, 2015; Wargovich, 2001). Additionally, the consumption of nuts has been shown to decrease the risk of developing colorectal cancer (Yang et al., 2015) as well as the risk of death from any cause (Bao et al., 2001). It is clear that a generally healthy lifestyle plays a role in decreased cancer risk and improved patient outcomes, and it may also be the case that consumption of specific compounds can alter these factors.

Coffee Consumption and Cancer

Coffee is one of the most commonly consumed beverages across the world and contains several antioxidants and other compounds that may play a role in cancer pathogenesis. Coffee is the largest source of dietary antioxidants in the United States (Bøhn et al., 2013), where 54% of adults reportedly consume coffee at least once per day (Harvard School of Public Health, 2015). Several lines of research suggest a relationship between coffee consumption and cancer, including colorectal cancer. A randomized study has shown a decreased risk of hepatocellular carcinoma among hepatitis C patients who consume coffee

(Cardin et al., 2013), and *in vitro* studies have shown anti-tumor cell activity associated with kahweol, a diterpene molecule found in coffee beans (Choi et al., 2015).

Epidemiological evidence points toward protective effects of coffee consumption against the risk of developing colorectal cancer. A recent prospective epidemiological study examined the influence of coffee, tea, and caffeine consumption in 953 patients with resected stage III colon cancer. The study found a significantly reduced risk of cancer recurrence and cancer mortality in patients who consumed 4 or more cups of coffee per day as compared to those who abstained (HR, 0.48; 95% CI, 0.25 to 0.91; $P_{trend} = .002$). Total caffeine intake was also associated with reduced risk of cancer recurrence and mortality (HR, 0.66; 95% CI, 0.47 to 0.93; $P_{trend} = .006$). These results remained consistent across other known predictors of cancer recurrence and mortality rates (Guercio et al., 2015).

Other epidemiological studies have found similar effects. One study conducted within a Japanese population noted a decreased risk of colorectal adenomas in coffee drinkers versus abstainers (Budhathoki et al., 2015). A meta-analysis of coffee-related studies in colorectal cancer conducted in 2013 found a nonlinear relationship between intakes of greater than 4 cups of coffee per day and reduced risk of colorectal cancer (Bøhn et al., 2013). Each of these previous studies examined the effects of coffee on primary colorectal cancer risk or cancer recurrence risk. To our knowledge, this is the first study to be conducted on the effects of coffee consumption in patients with metastatic disease.

Alliance/CALGB 80405

Alliance for Clinical Trials in Oncology, formerly known as Cancer and Leukemia Group B, is an NCI-funded cooperative group that conducts clinical trials and research in several types of cancer, including colorectal cancer. The group recently completed a large, multi-center, randomized trial comparing two approved biological therapies (bevacizumab versus cetuximab) in combination with standard chemotherapy regimens (Irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6), CALGB/SWOG 80405. The primary objective of the trial was to determine which chemotherapy/antibody combination conferred longer survival. Ultimately the results demonstrated that both regimens are equivalent; no significant difference in survival was detected between the two arms (Venook et al., 2014).

In addition to the demographics, treatment information, medical history, and disease information typically collected during the course of a clinical trial, participants in this study were asked to complete dietary and lifestyle questionnaires prior to initiating chemotherapy. The questionnaire asked patients to document their intake of greater than 100 food items (including coffee) as well as tobacco and alcohol use, over the counter drug use, physical activity, and other relevant behaviors. Previous research has demonstrated the validity of this questionnaire in large populations (see methods section) (Willett et al., 1985). Archival tumor samples were collected from all patients, and correlative research blood samples were drawn from patients prior to treatment initiation, 8 weeks after initiation, and at the time of disease progression or study termination. These biospecimens and surveys taken from a large cohort of metastatic colorectal cancer patients undergoing treatment with chemotherapy offer a unique opportunity to study lifestyle and molecular characteristics that may influence the

course of this disease. In light of the described research regarding coffee and the availability of this prospectively collected data, we conducted an epidemiological study within CALGB/SWOG 80405 examining the association of coffee intake with overall survival.

Chapter II

Methods

Study Participants

Prospectively collected data from a cohort of participants enrolled in CALGB/SWOG 80405 was analyzed in this study. The primary objective of the main clinical trial was to compare two approved metastatic colorectal cancer biologic therapies, cetuximab and bevacizumab, in combination with a standard chemotherapy backbone (Irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) (investigator choice)). When the trial was originally initiated, participants could be randomized to cetuximab, bevacizumab, or both. Based on emerging clinical data, after 1420 patients had accrued the study was amended such that only KRAS wild type tumors were included and the combination cetuximab plus bevacizumab arm was deleted (Venook et al., 2014). Eligible patients were required to have had no previous treatment for metastatic disease, no known concurrent cancers, adequate blood counts and organ function, good performance status, and willingness to sign informed consent (Venook et al., 2014). Patients were followed for both progression free survival and overall survival. Data collection and monitoring were conducted by the Alliance Statistics and Data Center.

The results of the overall trial did not show a significant difference between cetuximab- vs. bevacizumab-based treatment, indicating that either combination is appropriate for the treatment of first line KRAS wild-type metastatic colorectal cancer (Venook et al., 2014). Consequently, all patients were pooled for analysis of the primary objective.

Participants were excluded from our analysis if they did not complete a dietary questionnaire, left blank any of the questions related to coffee or tea, or reported significantly aberrant caloric intake (< 600 or > 4,200 calories/d for men; < 500 or > 3,500 calories/d for women). Participants were also excluded if they had cancer progression or death within 90 days of initiating treatment to avoid dietary assessment bias related to a decline in general health (Meyerhardt et al., 2012). After these exclusions, a total of 1160 patients were included in our analysis.

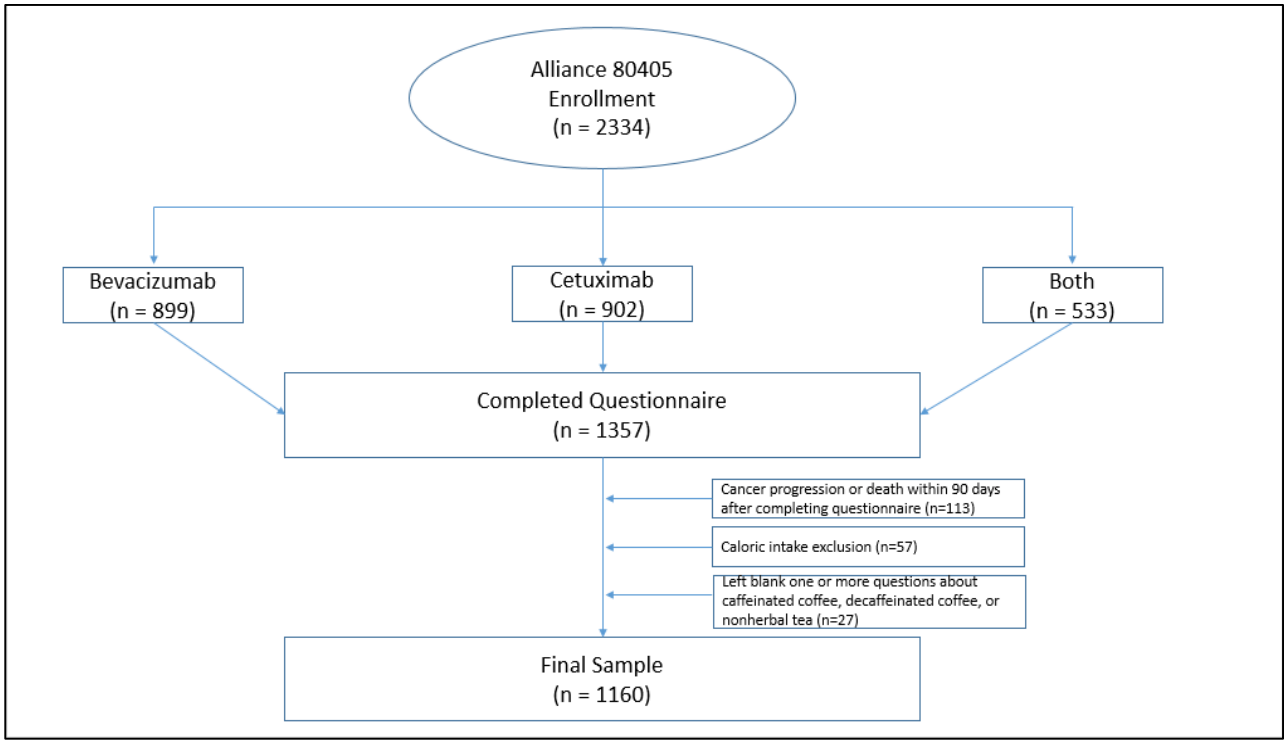


Figure 1: Description of the study population. Of the 2334 patients enrolled in this study, 1357 completed a lifestyle questionnaire. 113 of these were excluded due to cancer progression or death within 90 days of randomization, 57 were excluded due to significantly aberrant caloric intake (< 600 or > 4,200 calories/d for men; < 500 or > 3,500 calories/d for women), and 27 were excluded due to leaving blank one or more questions about coffee or tea consumption. The remaining 1160 patients comprised the final study population for this analysis.

Dietary Assessment

The diet and lifestyle questionnaire used in this study has been validated by previous studies in large populations (Willett et al., 1985), and many cancer-related epidemiological studies have been published using data collected in this manner (Meyerhardt et al., 2007; Meyerhardt et al., 2012; Fuchs et al., 2014; Guercio et al., 2015). The questionnaire is based on semi-quantitative questions that ask participants to indicate the frequency with which they consume 131 food items and vitamin/mineral supplements. Participants indicate how often, on average, during the previous 3 months, they consumed a specific food portion size, ranging from 0 to 6 times per day. Among these food items are caffeinated coffee, decaffeinated coffee, and non-herbal tea (Willett et al., 1985). Patients were divided into groups for analysis based on the numbers of cups of each beverage they reported per day.

Statistical Analysis

As noted above, no significant differences were detected between the two cancer therapy arms in this study, allowing us to pool patients from both arms. As was done in the stage III colon cancer recurrence study (CALGB 89803), intake of total coffee, caffeinated coffee, and tea were stratified into five frequency categories (0, < 1, 1, 2 to 3, and ≥ 4 cups/d) (Guercio et al., 2015). Herbal teas may contain different compounds with varying levels of biological activity, and therefore only non-herbal tea was included in our analysis (National Cancer Institute, 2010). Due to the limited number of participants who reported consumption of greater than 2 cups of decaffeinated coffee per day, more limited frequency categories were used for this exposure in order to preserve statistical power (0, < 1, 1, and ≥ 2 cups/d). This is

consistent with the data analysis done in the stage III cancer recurrence study (Guercio et al., 2015).

Cox proportional hazards regression was used to determine the effect of coffee and tea consumption on progression free survival and overall survival in our cohort of cancer patients (Cox, 1972). This type of analysis allowed us to control for other characteristics that can affect survival in colorectal cancer. We controlled for the following characteristics: total energy intake, sex, age, performance status, chemotherapy and biologic treatment arms, prior adjuvant chemotherapy, smoking history, alcohol consumption, body mass index, physical activity level, Western or prudent dietary pattern, glycemic load, sites of metastasis, and serum adiponectin level (a biomarker that was previously associated with coffee consumption and cancer progression) (Chong et al., 2015; Yamashita et al., 2012). All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC), and p values of .05 or less were considered statistically significant.

Chapter III

Results

Baseline Characteristics

Baseline characteristics by frequency of total coffee consumption are displayed in **Table 1**. Consistent with the findings from our analysis of coffee intake in stage III colon cancer patients, frequent coffee drinkers in this analysis were more likely to be white males. They were also more likely to be current or former smokers, had higher daily energy intake, and were more likely to follow a Western dietary pattern.

Table 1: Baseline Characteristics and Total Coffee Consumption of Study Cohort

	Coffee Intake (cups/day)				
Characteristics	**0 cups/d**	**<1 cups/d**	**1 cups/d**	**2-3 cups/d**	**>4 cups/d**
Total coffee					
N	278	297	297	226	62
Median (Range)	0.0 (0.0 - 0.0)	0.1 (0.0 - 0.5)	1.0 (0.5 - 1.4)	2.5 (1.6 - 3.3)	4.5 (3.5 - 12.0)
Age (years)					
Median (Range)	54 (22 - 84)	58 (21 - 82)	63 (24 - 85)	62 (36 - 82)	59 (42 - 82)
Gender, No. (%)					
Men	138 (49.6%)	176 (59.3%)	176 (59.3%)	140 (61.9%)	51 (82.3%)
Women	140 (50.4%)	121 (40.7%)	121 (40.7%)	86 (38.1%)	11 (17.7%)

Table 1: Baseline Characteristics and Total Coffee Consumption of Study Cohort					
	Coffee Intake (cups/day)				
Characteristics	**0 cups/d**	**<1 cups/d**	**1 cups/d**	**2-3 cups/d**	**>4 cups/d**
Race, No. (%)					
White	220 (79.1%)	234 (78.8%)	269 (90.6%)	214 (94.7%)	60 (96.8%)
Black	35 (12.6%)	52 (17.5%)	18 (6.1%)	7 (3.1%)	2 (3.2%)
Other	15 (5.4%)	8 (2.7%)	6 (2.0%)	3 (1.3%)	0 (0)
Unknown	8 (2.9%)	3 (1.0%)	4 (1.3%)	2 (0.9%)	0 (0)
Performance status, No. (%)					
ECOG 0	166 (59.7%)	179 (60.3%)	192 (64.6%)	144 (63.7%)	37 (59.7%)
ECOG 1	112 (40.3%)	118 (39.7%)	105 (35.4%)	82 (36.3%)	25 (40.3%)
Planned chemotherapy, No. (%)					
FOLFIRI	68 (24.5%)	54 (18.2%)	68 (22.9%)	51 (22.6%)	15 (24.2%)
FOLFOX	210 (75.5%)	243 (81.8%)	229 (77.1%)	175 (77.4%)	47 (75.8%)
Prior Adjuvant Chemo, No. (%)					
No	260 (93.5%)	271 (91.2%)	274 (92.3%)	205 (90.7%)	53 (85.5%)
Yes	18 (6.5%)	26 (8.8%)	23 (7.7%)	21 (9.3%)	9 (14.5%)
Assigned Treatment Arm, No. (%)					
Bevacizumab	101 (36.3%)	107 (36.0%)	120 (40.4%)	96 (42.5%)	24 (38.7%)
Cetuximab	102 (36.7%)	123 (41.4%)	105 (35.4%)	66 (29.2%)	26 (41.9%)
Bevacizumab + Cetuximab	75 (27.0%)	67 (22.6%)	72 (24.2%)	64 (28.3%)	12 (19.4%)

Table 1: Baseline Characteristics and Total Coffee Consumption of Study Cohort					
	Coffee Intake (cups/day)				
Characteristics	**0 cups/d**	**<1 cups/d**	**1 cups/d**	**2-3 cups/d**	**>4 cups/d**
Liver Metastasis, No. (%)					
No	58 (20.9%)	55 (18.5%)	69 (23.2%)	61 (27.0%)	23 (37.1%)
Yes	215 (77.3%)	234 (78.8%)	222 (74.7%)	162 (71.7%)	39 (62.9%)
Unknown	5 (1.8%)	8 (2.7%)	6 (2.0%)	3 (1.3%)	0 (0)
BMI (kg/m2)					
Median (Range)	27.9 (15.4 - 59.2)	27.3 (17.1 - 54.8)	27.2 (15.8 - 48.4)	27.2 (15.4 - 58.4)	27.4 (16.8 - 52.5)
Physical activity (Met-hr/wk)					
Median (Range)	3.8 (0.0 - 280.3)	3.4 (0.0 - 123.0)	3.2 (0.0 - 112.7)	4.5 (0.0 - 131.6)	3.4 (0.0 - 112.9)
Smoking, No. (%)					
Never	170 (61.2%)	149 (50.2%)	138 (46.5%)	55 (24.3%)	12 (19.4%)
Current	13 (4.7%)	18 (6.1%)	28 (9.4%)	41 (18.1%)	19 (30.6%)
Past	92 (33.1%)	128 (43.1%)	131 (44.1%)	129 (57.1%)	30 (48.4%)
Missing	3 (1.1%)	2 (0.7%)	0 (0)	1 (0.4%)	1 (1.6%)
Multivitamin use, No. (%)					
Never	83 (29.9%)	79 (26.6%)	83 (27.9%)	71 (31.4%)	24 (38.7%)
Past	72 (25.9%)	84 (28.3%)	69 (23.2%)	56 (24.8%)	13 (21.0%)
Current	117 (42.1%)	124 (41.8%)	127 (42.8%)	88 (38.9%)	25 (40.3%)

Table 1: Baseline Characteristics and Total Coffee Consumption of Study Cohort					
	Coffee Intake (cups/day)				
Characteristics	**0 cups/d**	**<1 cups/d**	**1 cups/d**	**2-3 cups/d**	**>4 cups/d**
Missing	6 (2.2%)	10 (3.4%)	18 (6.1%)	11 (4.9%)	0 (0)
Total energy consumed (kcal/day) *Median (Range)*	1706.6 (601.1 - 4038.3)	1714.3 (526.5 - 4012.4)	1819.8 (559.7 - 3945.8)	1972.2 (669.3 - 4087.8)	2235.2 (791.5 - 4121.6)
Alcohol (grams/d), energy-adjusted *Median (Range)*	0.0 (0.0 - 90.8)	0.4 (0.0 - 95.4)	1.1 (0.0 - 86.8)	1.1 (0.0 - 137.1)	0.7 (0.0 - 29.3)
Glycemic load, energy-adjusted *Median (Range)*	149.5 (39.9 - 249.9)	142.1 (77.5 - 245.9)	142.2 (79.3 - 217.5)	133.8 (57.3 - 212.7)	136.2 (93.9 - 192.7)
Glycemic index, energy-adjusted *Median (Range)*	56.3 (39.3 - 75.6)	54.9 (40.8 - 70.7)	54.8 (42.3 - 72.7)	53.9 (43.9 - 72.0)	54.3 (46.3 - 65.8)
Western dietary pattern, No. (%) *≥median*	103 (37.1)	122 (41.1)	148 (49.8)	155 (68.6)	54 (87.1)
Prudent dietary pattern, No. (%) *≥median*	122 (43.9)	142 (47.8)	160 (53.9)	123 (54.4)	27 (43.6)

Impact of Coffee Intake on Cancer Progression and Overall Survival

Increasing total coffee intake was associated with a significant decrease in the risk of both overall mortality and disease progression after adjusting for other variables that are associated with cancer prognosis. Participants who consumed 4 or more cups of coffee per day had an adjusted hazard ratio for mortality of 0.62 (95% CI, 0.43 to 0.89; Ptrend = 0.008) compared to patients who did not drink coffee. They also had an adjusted hazard ratio for disease progression of 0.71 (95% CI, 0.52 to 0.98; Ptrend = 0.04).

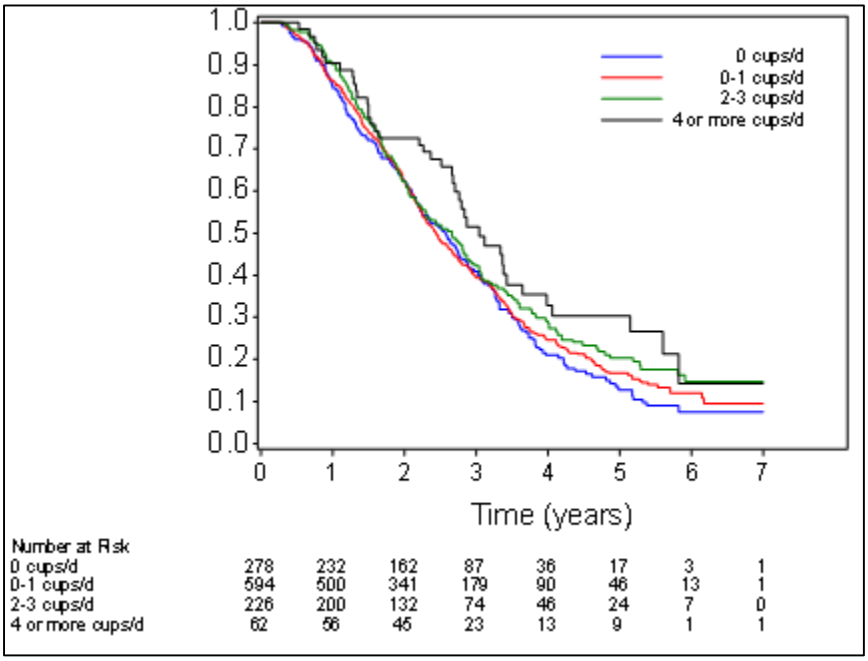
Improved outcomes were also found when caffeinated coffee and decaffeinated coffee were individually analyzed. Compared to abstainers, those who consumed 4 or more cups of caffeinated coffee per day had an adjusted hazard ratio for mortality of 0.67 (95% CI, 0.45 to 0.99; Ptrend = 0.05) and for disease progression of 0.76 (95% CI, 0.54 to 1.07; Ptrend = 0.03). Similarly, those who consumed 4 or more cups of decaffeinated coffee per day had an adjusted hazard ratio for mortality of 0.64 (95% CI, 0.41 to 0.98; Ptrend = 0.009). Consumption of decaffeinated coffee was not found to be significantly associated with progression-free survival. Consumption of non-herbal tea was not associated with any change in patient outcomes.

Table 2: Associations Between Progression Free Survival/Overall Survival and Total Coffee, Caffeinated Coffee, Decaffeinated Coffee, and Nonherbal Tea

Variable	Categories of Intake (cups/d)					P_{trend}‡
	0	<1	1	2-3	≥4	
Total coffee						
OS						
Events and total	211 of 278	215 of 297	217 of 297	162 of 226	40 of 62	-
HR (95% CI)						
Energy-adjusted *	1.0	0.94 (0.77-1.13)	0.97 (0.80-1.17)	0.86 (0.70-1.06)	0.70 (0.50-0.99)	**0.04**
MV-adjusted **	1.0	0.89 (0.73-1.09)	0.90 (0.74-1.10)	0.79 (0.63-0.99)	0.62 (0.43-0.89)	**0.008**
PFS						
Events and total	259 of 278	264 of 297	269 of 297	202 of 226	53 of 62	
HR (95% CI)						
Energy-adjusted *	1.0	0.88 (0.74-1.05)	0.94 (0.79-1.11)	0.86 (0.71-1.03)	0.79 (0.58-1.06)	0.13
MV-adjusted **	1.0	0.85 (0.71-1.02)	0.89 (0.74-1.06)	0.79 (0.65-0.97)	0.71 (0.52-0.98)	**0.04**
Caffeinated coffee						
OS						
Events and total	275 of 376	269 of 359	128 of 178	141 of 197	32 of 50	-
HR (95% CI)						
Energy-adjusted *	1.0	1.03 (0.87-1.22)	1.10 (0.89-1.36)	0.94 (0.76-1.15)	0.77 (0.53-1.11)	0.15
MV-adjusted **	1.0	0.99 (0.83-1.19)	1.11 (0.89-1.38)	0.89 (0.71-1.11)	0.67 (0.45-0.99)	**0.05**
PFS						
Events and total	345 of 376	324 of 359	160 of 178	175 of 197	43 of 50	-
HR (95% CI)						
Energy-adjusted *	1.0	0.95 (0.81-1.11)	1.02 (0.84-1.23)	0.85 (0.70-1.02)	0.85 (0.61-1.17)	0.09
MV-adjusted **	1.0	0.93 (0.79-1.09)	1.00 (0.82-1.22)	0.80 (0.66-0.98)	0.76 (0.54-1.07)	**0.03**
Decaffeinated coffee						
OS	599 of 821	194 of 262	30 of 44	22 of 33		-
Events and total						
HR (95% CI)						
Energy-adjusted *	1.0	0.98 (0.83-1.15)	0.73 (0.50-1.05)	0.66 (0.43-1.02)		**0.02**
MV-adjusted **	1.0	0.94 (0.79-1.11)	0.69 (0.47-1.00)	0.64 (0.41-0.98)		**0.009**
PFS						
Events and total	743 of 821	238 of 262	37 of 44	29 of 33		-
HR (95% CI)						
Energy-adjusted *	1.0	1.03 (0.89-1.19)	0.87 (0.62-1.21)	0.97 (0.67-1.40)		0.62
MV-adjusted **	1.0	1.01 (0.87-1.18)	0.83 (0.60-1.17)	0.94 (0.64-1.37)		0.47
Nonherbal tea						
OS						
Events and total	329 of 448	418 of 568	49 of 75	49 of 69		-
HR (95% CI)						
Energy-adjusted *	1.0	1.02 (0.88-1.18)	0.95 (0.70-1.29)	1.01 (0.75-1.36)		0.89
MV-adjusted **	1.0	1.01 (0.88-1.17)	0.95 (0.70-1.29)	1.01 (0.74-1.38)		0.93
PFS						
Events and total	399 of 448	515 of 568	70 of 75	63 of 69		-
HR (95% CI)						
Energy-adjusted *	1.0	1.06 (0.93-1.21)	1.01 (0.78-1.30)	0.99 (0.76-1.29)		0.74
MV-adjusted **	1.0	1.05 (0.92-1.20)	1.00 (0.78-1.30)	1.00 (0.76-1.31)		0.84

Abbreviations: PFS, progression free survival; OS overall survival; HR, hazard ratio
‡ Two Sided P Value; Trend across consumption levels
* Adjusted for participants' energy intake (kcal/d, continuous)
** Adjusted for total energy intake (kcal/d, continuous), sex, age (years, continuous), performance status (0,1,2), planned chemotherapy (FOLFIRI, FOLFOX), prior adjuvant chemotherapy (yes, no), assigned treatment arm (bevacizumab, cetuximab, both), smoking history (never, past, current, missing), alcohol consumption (continuous, grams/d), body mass index (continuous, kg/m^2), physical activity level (continuous, or missing), Western dietary pattern (continuous), prudent dietary pattern (continuous), glycemic load (continuous), liver metastasis (yes, no, or missing)

A



B

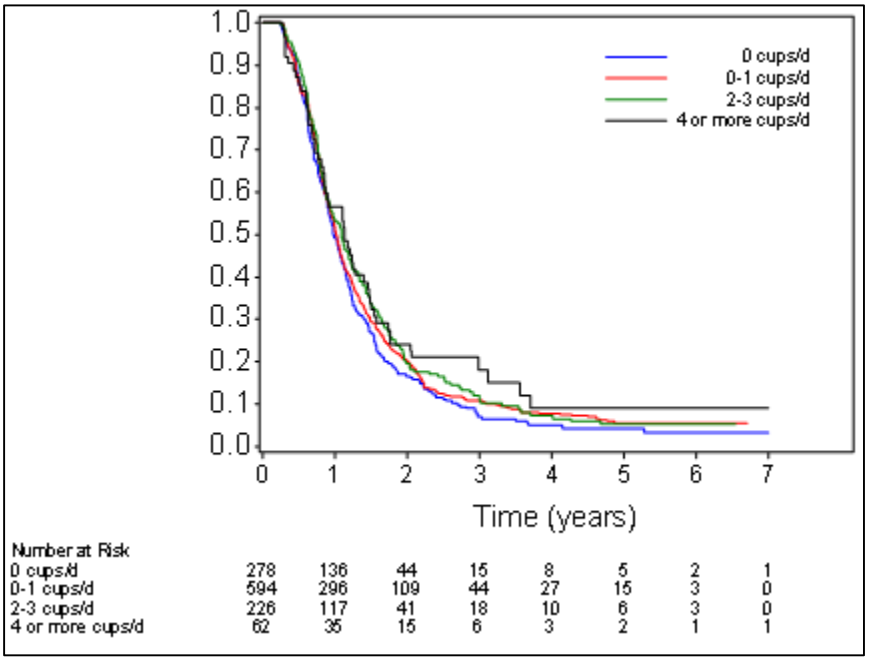


Figure 2: (A) Overall survival according to consumption of total coffee. (B) Progression-free survival according to consumption of total coffee.

Stratified Analysis

We additionally analyzed the influence of total coffee consumption on overall survival and progression free survival across strata of other potential predictors of patient outcome. The trend of decreased risk of death or disease progression with increasing coffee consumption appeared to remain consistent across strata of most patient, disease, and treatment variables (Tables 3 and 4, respectively). The association between decreased risk of disease progression and increased coffee consumption was found to be stronger in patients who were more adherent to a prudent dietary pattern ($P_{interaction} = 0.03$). No other significant interactions were detected.

Table 3. Subgroup Analysis of the associations between total coffee and multivariable-adjusted overall survival (OS)

Subgroup	# of Patients	Q1 (n=208)	Q2 (n=209)	Q3 (n=208)	Q4 (n=210)	Q5 (n=208)	$P_{interaction}$
Age (years)							
< 60	625	1 (Referent)	0.88 (0.68-1.12)	0.79 (0.60-1.04)	0.74 (0.54-1.01)	0.54 (0.32-0.90)	0.54
≥ 60	535	1 (Referent)	0.95 (0.68-1.32)	1.08 (0.78-1.48)	0.89 (0.62-1.27)	0.77 (0.45-1.34)	
Sex							
Male	681	1 (Referent)	0.87 (0.66-1.14)	0.84 (0.63-1.12)	0.81 (0.59-1.11)	0.59 (0.38-0.92)	0.69
Female	479	1 (Referent)	0.96 (0.71-1.29)	1.03 (0.76-1.38)	0.73 (0.51-1.04)	0.70 (0.33-1.46)	
ECOG performance status							
0	718	1 (Referent)	0.79 (0.61-1.03)	0.89 (0.68-1.16)	0.74 (0.55-1.00)	0.70 (0.43-1.14)	0.63
1	442	1 (Referent)	1.06 (0.79-1.44)	0.98 (0.71-1.35)	0.88 (0.61-1.26)	0.57 (0.33-1.01)	
Planned chemotherapy							
FOLFIRI	256	1 (Referent)	0.90 (0.54-1.49)	0.84 (0.52-1.34)	0.78 (0.45-1.33)	0.62 (0.26-1.51)	0.89
FOLFOX	904	1 (Referent)	0.93 (0.74-1.15)	0.94 (0.75-1.17)	0.78 (0.60-1.00)	0.63 (0.42-0.95)	
Assigned treatment arm							
Bevacizumab	448	1 (Referent)	0.85 (0.60-1.21)	0.96 (0.67-1.36)	0.88 (0.60-1.29)	1.00 (0.52-1.92)	0.15
Cetuximab	422	1 (Referent)	1.05 (0.75-1.48)	0.99 (0.69-1.40)	1.17 (0.77-1.77)	0.53 (0.28-0.99)	
Both	290	1 (Referent)	0.74 (0.51-1.08)	0.80 (0.55-1.17)	0.47 (0.31-0.73)	0.43 (0.21-0.88)	
Body mass index (kg/m2)							
<25	354	1 (Referent)	0.68 (0.48-0.97)	0.77 (0.53-1.10)	0.65 (0.42-0.99)	0.25 (0.12-0.53)	0.07
≥25	806	1 (Referent)	0.99 (0.78-1.26)	0.97 (0.76-1.24)	0.84 (0.64-1.11)	0.90 (0.59-1.38)	
Physical activity							
< median	577	1 (Referent)	1.10 (0.84-1.45)	1.18 (0.89-1.56)	0.91 (0.65-1.26)	0.86 (0.54-1.38)	0.75
≥ median	580	1 (Referent)	0.72 (0.54-0.96)	0.69 (0.51-0.93)	0.71 (0.52-0.98)	0.43 (0.24-0.77)	
Glycemic load							
<median	580	1 (Referent)	0.94 (0.69-1.27)	0.81 (0.59-1.09)	0.89 (0.65-1.23)	0.72 (0.45-1.16)	0.86
≥median	580	1 (Referent)	0.82 (0.62-1.07)	0.96 (0.73-1.27)	0.64 (0.45-0.91)	0.44 (0.24-0.81)	
Western dietary pattern							
<median	580	1 (Referent)	0.95 (0.74-1.24)	1.06 (0.81-1.39)	0.83 (0.58-1.19)	0.41 (0.16-1.03)	0.71
≥median	580	1 (Referent)	0.83 (0.61-1.13)	0.80 (0.59-1.08)	0.74 (0.54-1.02)	0.63 (0.41-0.96)	
Prudent dietary pattern							
<median	580	1 (Referent)	1.06 (0.80-1.39)	0.95 (0.71-1.28)	0.89 (0.64-1.23)	0.69 (0.42-1.14)	0.68
≥median	580	1 (Referent)	0.77 (0.57-1.03)	0.87 (0.66-1.16)	0.68 (0.49-0.94)	0.57 (0.33-0.99)	

Pinteraction = two-sided P value; trend across consumption levels

Multivariable model adjusted for age, gender, performance status (0,1), planned chemotherapy (FOLFIRI, FOLOFOX), prior adjuvant chemotherapy (yes, no), assigned treatment arm (bevacizumab, cetuximab, both), BMI (continuous), physical activity (continuous, missing as a dummy variable), race (White, Black, Other, Unknown), season (Winter, Spring, Summer, Fall, Missing), region (Canada: Northeast, Midwest/west; United States: Northeast, Midwest/west, South) and RAS mutation status (wild-type, mutant, unknown)

Table 4. Subgroup Analysis of the associations between total coffee and multivariable-adjusted progression free survival (PFS)

Subgroup		# of Patients	Q1 (n=208)	Q2 (n=209)	Q3 (n=208)	Q4 (n=210)	Q5 (n=208)	$P_{interaction}$
Age (years)								
	< 60	625	1 (Referent)	0.88 (0.71-1.10)	0.70 (0.54-0.89)	0.75 (0.57-0.98)	0.65 (0.43-0.98)	0.32
	≥ 60	535	1 (Referent)	0.81 (0.60-1.10)	1.11 (0.83-1.49)	0.85 (0.61-1.18)	0.79 (0.47-1.34)	
Sex								
	Male	681	1 (Referent)	0.86 (0.67-1.09)	0.86 (0.67-1.10)	0.91 (0.69-1.21)	0.78 (0.53-1.14)	0.09
	Female	479	1 (Referent)	0.92 (0.70-1.21)	1.02 (0.78-1.35)	0.70 (0.51-0.96)	0.64 (0.31-1.32)	
ECOG performance status								
	0	718	1 (Referent)	0.73 (0.58-0.92)	0.81 (0.64-1.02)	0.72 (0.56-0.93)	0.77 (0.51-1.17)	0.39
	1	442	1 (Referent)	1.05 (0.79-1.39)	1.03 (0.76-1.39)	0.86 (0.61-1.20)	0.64 (0.38-1.08)	
Planned chemotherapy								
	FOLFIRI	256	1 (Referent)	0.90 (0.59-1.37)	1.15 (0.76-1.75)	0.95 (0.59-1.51)	0.88 (0.41-1.88)	0.81
	FOLFOX	904	1 (Referent)	0.88 (0.72-1.07)	0.86 (0.70-1.06)	0.78 (0.62-0.99)	0.73 (0.51-1.04)	
Assigned treatment arm								
	Bevacizumab	448	1 (Referent)	0.85 (0.63-1.15)	0.96 (0.71-1.30)	0.87 (0.62-1.21)	1.20 (0.71-2.04)	0.42
	Cetuximab	422	1 (Referent)	0.83 (0.61-1.12)	0.89 (0.66-1.22)	0.79 (0.55-1.14)	0.49 (0.29-0.84)	
	Both	290	1 (Referent)	0.90 (0.63-1.29)	0.76 (0.53-1.09)	0.66 (0.44-0.99)	0.66 (0.33-1.31)	
Body mass index (kg/m2)								
	<25	354	1 (Referent)	0.82 (0.59-1.15)	0.92 (0.65-1.29)	0.63 (0.41-0.95)	0.41 (0.22-0.76)	0.09
	≥25	806	1 (Referent)	0.86 (0.69-1.06)	0.87 (0.70-1.09)	0.83 (0.66-1.05)	0.84 (0.58-1.23)	
Physical activity								
	< median	577	1 (Referent)	0.98 (0.76-1.26)	1.00 (0.77-1.30)	0.79 (0.58-1.06)	0.93 (0.60-1.44)	0.45
	≥ median	580	1 (Referent)	0.77 (0.60-1.00)	0.76 (0.59-0.99)	0.78 (0.59-1.03)	0.55 (0.34-0.88)	
Glycemic load								
	<median	580	1 (Referent)	0.97 (0.73-1.27)	0.90 (0.68-1.19)	0.92 (0.69-1.24)	0.86 (0.56-1.31)	0.35
	≥median	580	1 (Referent)	0.78 (0.61-0.99)	0.92 (0.72-1.17)	0.70 (0.51-0.94)	0.53 (0.32-0.90)	
Western dietary pattern								
	<median	580	1 (Referent)	0.88 (0.69-1.10)	0.96 (0.76-1.23)	0.86 (0.62-1.18)	0.46 (0.20-1.05)	0.65
	≥median	580	1 (Referent)	0.89 (0.67-1.18)	0.85 (0.64-1.13)	0.78 (0.59-1.04)	0.78 (0.54-1.13)	
Prudent dietary pattern								
	<median	580	1 (Referent)	0.89 (0.70-1.14)	1.03 (0.80-1.35)	1.00 (0.75-1.34)	0.94 (0.62-1.44)	0.01
	≥median	580	1 (Referent)	0.79 (0.61-1.03)	0.78 (0.60-1.02)	0.65 (0.49-0.88)	0.54 (0.33-0.89)	

Pinteraction = two-sided P value; trend across consumption levels

Adjusting with Cox proportional hazards regression for age, gender, performance status (0,1,2), planned chemotherapy (FOLFIRI, FOLOFOX), prior adjuvant chemotherapy (yes, no), assigned treatment arm (bevacizumab, cetuximab, both), BMI (continuous), physical activity (continuous, missing as a dummy variable), race (White, Black, Other, Unknown), season (Winter, Spring, Summer, Fall, Missing), region (Canada: northeast, Midwest/west; United States: Northeast, Midwest/west, South) and RAS mutation status (wild-type, mutant, unknown)

Chapter IV

Discussion

The results from this prospective epidemiological study were consistent with our hypothesis: increased consumption of coffee was associated with a significant improvement in both progression free survival and overall survival in metastatic colorectal cancer patients. Unlike the previous study on cancer recurrence in patients who had been treated for stage III colon cancer, which found a benefit for caffeinated coffee only, this study found similar results for both caffeinated and decaffeinated coffee consumption. These associations were consistent across participant, disease, and treatment characteristics and remained significant after controlling for other factors known or suspected to affect survival in colorectal cancer patients. A significant interaction was detected between coffee consumption and patients' adherence to prudent dietary patterns, two factors previously correlated with colorectal cancer development and outcomes (Hartz et al., 2012; Meyerhardt et al., 2007; Platz et al., 2000).

Previous studies, including the study that examined coffee consumption in stage III colon cancer, have proposed that coffee may act to reduce colorectal cancer recurrence through caffeine's insulin sensitizing and anti-hyperinsulinemia effects. This hypothesis is primarily based on studies that have linked high energy states to cancer progression and mortality, and is supported by the finding in our previous study that only caffeinated coffee intake was significantly associated with decreased mortality (Meyerhardt et al., 2007; Meyerhardt et al., 2012; Fuchs et al., 2014; Guercio et al., 2015). Interestingly, the present study found a statistically significant decrease in mortality in both caffeinated coffee and

decaffeinated coffee drinkers, suggesting that caffeine may not be the only molecule conferring a protective effect. Although several studies have demonstrated an inverse relationship between caffeine itself and insulin levels, as well as between caffeine and the risk of type 2 diabetes, several prospective studies and meta-analyses have also shown a relationship between decaffeinated coffee and the insulin pathway (Keijzers et al., 2002; Ding et al., 2014). For example, another prospective study found a decrease in hemoglobin A1c, a marker of diabetes, associated with decaffeinated coffee (Zhang et al., 2009). It is therefore reasonable to conclude that both caffeine and other compounds found in coffee may play a role in its protective effect. One such candidate is chlorogenic acid, which has been shown to modify glucose levels and tolerance in humans and rats (Tunnicliffe et al., 2011; Johnston et al., 2003).

Besides its insulin-sensitizing effects, coffee may contain molecules that slow tumor growth via other mechanisms. Coffee is the largest source of dietary antioxidants in the United States (Bøhn et al., 2013). One such antioxidant, kahweol, has been shown to slow the growth of tumor cells in vitro, an effect that may be mediated by kahweol's anti-inflammatory and anti-angiogenic effects (Choi et al., 2015; Cárdenas et al., 2011). Previous studies have implicated high oxidative stress in colorectal carcinoma development and metastases (Babbs, 1990; Baltruskeviciene, 2016; Gackowski et al., 2002). As such, a greater consumption of antioxidants could reasonably be hypothesized to slow the development of such cancers. In support of this possibility, the current study detected a greater benefit of coffee consumption a prudent diet, which is comprised of foods that contain higher concentrations of antioxidants. Coffee consumption has also been associated with anti-inflammatory and pro-apoptotic effects that may decrease mutagenesis and cancer progression (Lopez-Garcia et al., 2006;

Bøhn et al., 2013). Further research is ongoing to identify the specific molecules found in coffee and their impact on cancer treatment and survival in human patients.

These results remained statistically significant after controlling for gender, age, performance status, planned chemotherapy, prior adjuvant chemotherapy, assigned treatment arm, smoking history, alcohol consumption, total energy intake, body mass index, physical activity level, Western dietary pattern, prudent dietary pattern, glycemic load, and the presence of liver metastases. However, despite this adjustment, it remains possible that our results were confounded by factors that were not captured in the clinical trial or associated questionnaire, such as sleep habits, employment, or physical activity not related to dedicated exercise hours. Furthermore, most patients who consume coffee while being treated for cancer likely consumed coffee before cancer diagnosis, so we cannot discern whether the consumption of coffee acts directly on active tumors or whether coffee drinkers tend to develop less aggressive tumors. However, either of these possibilities would suggest a role for compounds found in coffee in colorectal cancer outcomes. Finally, it is possible that the population of cancer patients enrolled on Alliance 80405 is not representative of the general population of colorectal cancer patients. However, this clinical trial recruited patients from both academic and community hospitals across the United States, and similar randomized clinical trials are routinely used to determine the standards of care for treatment of colorectal and other forms of cancer.

In conclusion, this large prospective epidemiological study detected an association between improved colorectal cancer outcomes and the increased consumption of coffee. The effect was strongest in patients who drank ≥4 cups of coffee per day and in patients who closely adhered to a prudent dietary pattern. These findings confirm the relationship between

coffee consumption and colorectal cancer outcomes that has been described by previous epidemiological studies, though this is the first such study done in patients with active, metastatic colorectal cancer. Further research is needed to elucidate the specific mechanism driving these associations.

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